

Human Vaccines: News

Proof of efficacy shown for Sanofi Pasteur's dengue vaccine

Sanofi Pasteur, the vaccines division of Sanofi, recently announced that its tetravalent live attenuated dengue vaccine candidate demonstrated excellent safety and proof of efficacy against dengue in the world's first ever dengue efficacy trial, conducted in Thailand.

Dengue fever is a mosquito-borne disease caused by four types of dengue virus (types 1 to 4). It is estimated that the disease is a potential threat to almost half of the world's population; some individuals, mostly children, may develop dengue hemorrhagic fever, a severe and often fatal form of the disease. Dengue is prevalent in many countries of Latin America and Asia, where epidemics occur, but it is expanding geographically, as was shown by a recent outbreak in Florida (US).

Sanofi Pasteur's investigational dengue vaccine targets all four virus types. It has successfully passed phase 1 and 2 in adults and children in the US, Asia and Latin America. Overall, an immune response against all four

serotypes was observed after three doses of the vaccine. Currently, large-scale Phase 3 trials in 31,000 adults and children are ongoing in 10 countries in Latin America and Asia.

The study in Thailand included about 4,000 children between 4 and 11 years of age, and was conducted in partnership with the Mahidol University under the patronage of the Thai Ministry of Public Health in Muang district of the Ratchaburi Province. Study subjects received 3 doses of the vaccine at 0, 6 and 12 months.

The vaccine was safe and generated antibody response for all four dengue virus serotypes. Evidence of protection was demonstrated against three of the four virus serotypes circulating in Thailand. Analyses are ongoing to better understand the lack of protection for the fourth serotype in the particular epidemiological context of Thailand. Detailed results of the study are expected to be published later this year.

"Results of this first efficacy trial with Sanofi Pasteur's dengue vaccine candidate represent a key milestone in the quest to develop a safe and efficacious human vaccine against dengue," said Dr. Michel De Wilde, Executive Vice President, Research & Development, Sanofi Pasteur. "This is also an important development for global public health, since there is currently no specific treatment or prevention for dengue. We are fully committed to making dengue a vaccine-preventable disease by bringing a safe and effective vaccine to people living in endemic regions of the world."

The US Food and Drug Administration (FDA) has granted fast-track designation to Sanofi's investigational dengue vaccine, which is the leading dengue vaccine candidate in development. The FDA fast-track designation recognizes that a dengue vaccine would address an important unmet medical need for a serious disease.

Multi-peptide therapeutic Renal Cell Carcinoma vaccine shows clinical benefit

Positive results of a phase 1 and a phase 2 trial with immatics' renal cell carcinoma (RCC) vaccine IMA901 were recently published in the journal *Nature Medicine*.¹ The vaccine is being evaluated in a pivotal randomized controlled Phase 3 clinical study in combination with sunitinib, the standard first-line therapy in RCC marketed by Pfizer.

The German clinical-stage biopharmaceutical company immatics biotechnologies develops advanced therapeutic vaccines for the treatment of cancer. Its lead product IMA901 consists of 10 tumor-associated peptides (TUMAPs) confirmed to be naturally presented on tumor cells in patients with RCC. The peptides were identified, selected and validated using immatics' proprietary XPRESIDENT platform, which offer a uniquely rational approach to cancer vaccine development.

The results of the two clinical trials with IMA901 in 96 RCC patients showed that

subjects achieve better clinical benefit (extended survival) if they are able to mount immune responses to multiple peptides in the vaccine. This confirms the hypothesis that a broad attack of the immune system on multiple targets simultaneously is beneficial. In addition, the randomized phase 2 trial demonstrated that a single dose of cyclophosphamide given prior to the first vaccination with IMA901 reduces the numbers of regulatory T cells (Tregs) and is associated with a better overall outcome. Tregs are thought to counteract the anti-tumor response of cancer vaccines. The *Nature Medicine* paper also describes the work to identify serum biomarkers to help predict which patients could achieve overall survival benefit in future studies with IMA901. Two potential biomarkers, apolipoprotein A-1 and chemokine (C-C motif) ligand 17, were identified, and are now being validated in the current pivotal phase 3 trial. And finally, for the

first time in RCC patients, the clinical relevance of certain types of myeloid-derived suppressor cells, a novel type of regulatory cell counteracting cancer immunotherapy, was described.

Dr. Paul Higham, immatics' Chief Executive Officer, said: "The potential of IMA901 to extend survival times for patients with renal cancer while offering a very good side effect profile is very exciting and offers the potential of real clinical benefit to patients with RCC. Our results so far illustrate the power of our rational approach to cancer vaccine development. We look forward to confirming the positive findings we have generated when we report the results from our on-going pivotal phase 3 trial with IMA901."

Reference

1. Walter S, et al. *Nat Med* 2012; 18:1254-1261.

Poor sleep can reduce effectiveness of vaccines

A new study, published in the journal *Sleep*,¹ shows that sleep duration is directly tied to vaccine immune response. In particular, the researchers found that poor sleep patterns can reduce the effectiveness of vaccines.

“With the emergence of our 24-h lifestyle, longer working hours, and the rise in the use of technology, chronic sleep deprivation has become a way of life for many Americans,” said study lead author Dr. Aric Prather from the University of California, San Francisco. “These findings should help raise awareness in the public health community about the clear connection between sleep and health.”

It is widely accepted that poor sleep can increase susceptibility to illnesses such as upper respiratory tract infections. The new study, conducted at the University of Pittsburgh set out to explore whether sleep duration, sleep efficiency, and sleep quality

—assessed at home and not in a controlled sleep lab—would impact immune processes important in the protection against infection. To this end, 125 healthy adults, all non-smokers and living in Pennsylvania, received the standard three-dose hepatitis B vaccine at 0, 1 and 6 months. Antibodies were measured prior to the second and third vaccine injection and six months after the final vaccination to determine whether participants had mounted a clinically protective response. All participants completed sleep diaries detailing their bedtime, wake time and sleep quality, and 88 subjects also wore electronic sleep monitors known as actigraphs.

The researchers found that people who slept fewer than six hours on average per night were far less likely to mount effective antibody responses to the vaccine and thus were far

more likely (11.5 times) to be left unprotected by vaccination than people who slept more than seven hours on average. Sleep quality did not affect response to vaccinations. Of the 125 participants, 18 did not receive adequate protection from the vaccine.

The authors conclude that short sleep duration in the natural environment may negatively affect in vivo antibody responses to novel antigens, providing a possible explanation for observed associations of poor sleep with increased susceptibility to infectious disease. “Based on our findings and existing laboratory evidence, sleep may belong on the list of behavioral risk factors that influence vaccination efficacy,” said Dr. Prather.

Reference

1. Prather AA, et al. *Sleep* 2012; 35:1063-9.

Innovative grass pollen allergy vaccine positive in phase 2

The Austrian biopharmaceutical company Biomay AG recently announced promising results from a first-in-man phase 2a trial with its innovative allergy vaccine BM32. The vaccine significantly reduced allergy-related nasal symptoms in patients suffering from grass pollen allergy.

In the industrialized world up to 25% of the overall population are affected by allergies, and more than half of these patients suffer from grass pollen allergy, commonly known as hay fever. This disease severely affects the well-being of patients and their daily activities, and causes immense overall healthcare costs. Immunotherapy is the only causal treatment for allergies, but continues to have low acceptance due to inconvenient dosing and a poor side effect profile.

BM32 is based on an innovative recombinant peptide carrier technology that allows

fewer injections and shows fewer side effects compared to other immunotherapy treatments for allergy sufferers. The phase 2a trial included 70 patients with grass pollen allergy. They received three doses of BM32 or a placebo by subcutaneous injections over a period of two months. Allergy-related nasal symptoms were significantly reduced in the vaccinated group, and the environmental challenge study also showed that BM32 reduced skin reactivity to grass pollen as demonstrated by skin prick testing. The treatment was safe and well-tolerated, even though a full dose of vaccine was given from the first day of treatment.

Dr. Rainer Henning, CEO of Biomay, commented: “We are very encouraged by these exciting data. They validate our scientific hypothesis that Biomay’s proprietary recombinant peptide carrier technology can form the basis of vaccines that induce the production

of protective antibodies against allergenic proteins contained in grass pollen, which are the root cause of the disease. At the same time, this technology reduces the risk of side effects and the need for multiple injections.”

Biomay has already initiated a phase 2b trial for its lead candidate BM32 with 180 allergic patients. Eleven leading allergy centers across Europe have agreed to participate in this new trial to test BM32 under natural pollen exposure over two pollen seasons. A team led by Professor Rudolf Valenta at the Medical University Vienna (Austria) has started to develop similar vaccines for the other major causes of allergies in partnership with Biomay. This project includes vaccines against allergies caused by house dust mites, other pollen, mold and pets.

GSK’s shingles vaccine starts phase 3 in immunocompromised patients

A new herpes zoster candidate vaccine will be tested in a phase 3 trial for the prevention of shingles in immunocompromised patients. The vaccine candidate HZ/su, developed by GlaxoSmithKline (GSK), contains the adjuvant

QS-21 Stimulon that is proprietary to the biotechnology company Agenus Inc.

The disease shingles, also known as herpes zoster, causes a painful skin rash. In addition, shingles can lead to severe pain that can last

for months or even years after the rash has gone, a condition known as post-herpetic neuralgia. The disease is caused by the varicella zoster virus (VZV), the same virus that causes chickenpox. After a person recovers from

chickenpox, the virus remains in the nerve tissue of the body in a dormant state, and years later can reactivate as shingles. Especially older people and immunocompromised individuals are at risk of developing shingles.

The immunocompromised study is part of a phase 3 clinical program that began in August 2010. This program includes a global, randomized, placebo-controlled phase 3 clinical trial of HZ/su formulated with QS-21 in 30,000 adult subjects. The immunocompromised study will include approximately 200

clinical sites and enroll more than 1,400 subjects 18 years of age and older who are undergoing hematopoietic stem cell transplantation (HCT). Shingles can occur as a complication of HCT, and limited treatment and prevention options are available.

The adjuvant used in the study, QS-21, is one of the most widely tested vaccine adjuvants under development. It is a key component in a number of investigational vaccine formulations addressing a variety of indications, including infectious diseases, cancers and

degenerative disorders. Examples besides the shingles vaccine HZ/su include GSK's RTS,S for malaria, GSK's MAGE-A3 cancer immunotherapies for melanoma or small cell lung cancer, and Janssen's ACC-001 for Alzheimer's disease.

"There are 16 QS-21 containing vaccines in clinical development, and we look forward to significant news flow from our partners with pivotal data readouts expected from at least four key clinical programs that incorporate QS-21," said Dr. Garo Armen, chairman and CEO of Aenus.

Overweight? There may be vaccine for that

Two vaccine candidates promote weight loss in mice, according to a new study published in the *Journal of Animal Science and Biotechnology*.¹

Obesity and obesity-related disease are a growing health issue worldwide. The peptide hormone somatostatin inhibits the action of growth hormone (GH) and insulin-like growth factor (IGF-1), both of which increase metabolism and result in weight loss. Vaccination with modified somatostatin causes the body to generate antibodies to somatostatin, effectively removing this inhibition without directly interfering with the growth hormones and subsequently increasing energy expenditure and weight loss.

Dr. Keith Haffer from Braasch Biotech LLC (SD, USA) assessed the effectiveness of two somatostatin vaccine candidates formulated with different adjuvants (JH17 or JH18) in reducing weight gain and increasing weight loss in mice. Animals in all groups had been fed a high fat diet for eight weeks prior to the study and continued to eat the same food for the duration of the six-week study. At Day 1 and Day 22 of the study, three groups of ten mice each received JH17, JH18 or placebo by intraperitoneal injection. Four days after the first injection of modified somatostatin, a 10% drop in body weight was observed in vaccinated mice compared to control animals. At the end of the study, results showed that both

vaccine formulations induced antibodies to somatostatin and significantly reduced body weight, sustaining a 10% lower body weight without affecting normal levels of the growth hormone IGF-1 or insulin levels.

"This study demonstrates the possibility of treating obesity with vaccination", Dr. Haffer explained. "Although further studies are necessary to discover the long term implications of these vaccines, treatment of human obesity with vaccination would provide physicians with a drug- and surgical- free option against the weight epidemic."

Reference

1. Haffer KN. *J Anim Sci Biotechnol* 2012; 3:21.

Vaccination records available online

The Indiana State Department of Health (IN, USA) has recently unveiled a new online tool called "MyVaxIndiana", which provides residents of Indiana direct access to their immunization records.

"Our goal is to further improve immunization rates of Hoosiers [residents of Indiana] by providing parents and patients ready on line access to their own vaccine records, 24 /7," said State Health Commissioner Dr. Gregory Larkin. "Having both the health care provider and the patient completely understand what vaccines have been given and what

are further recommended will add to vaccine compliance."

Indiana residents may access their immunization records on the secure website by entering their date of birth and a personal identification number, which must be requested from their healthcare provider or local health department in advance. Immunization history, as well as the Centers for Disease Control and Prevention's (CDC's) Advisory Committee for Immunization Practices (ACIP) schedule, can then be viewed, with the option to download, print, or fax the record.

All MyVaxIndiana records appear as they are maintained in the Indiana Children and Hoosiers Immunization Registry Program (CHIRP), which is supported by the CDCP. Currently, CHIRP contains about 4 million "active" records, which are defined as having two or more vaccines entered. The goals of the new MyVaxIndiana tool are to improve state immunization rates, to empower residents to become a partner in managing their healthcare, and to reduce the burden of office visits.

US females often do not complete HPV vaccination regimens

Vaccination rates for human papilloma virus (HPV) vaccine remain low in the United States; in particular, the recommended 3-dose regimen is often not completed. A study published in the Centers for Disease Control's *Morbidity and Mortality Weekly Report*¹ drew on data from the 2010 National Immunization Survey-Teen, and showed that only 32% of US females aged 13-17 received all three doses of the HPV vaccine.

Both licensed HPV vaccines, Gardasil (Merck) and Cervarix (GlaxoSmithKline), employ a three-dose regimen designed to protect patients against HPV, a sexually transmitted virus that can cause genital warts or cervical and anal cancers. Both vaccines are approved for use in females, and Gardasil is also approved for use in males. One important reason for vaccinating males, besides protecting them from genital warts, is to prevent them from transmitting HPV to females.

Unlike in some other countries, for example Australia, HPV vaccination is not mandatory in most US states. This means that subjects

sometimes take one or two shots of the series and do not come back for the remaining doses. While receiving fewer than three doses is not ideal, it is better than receiving none, said Dr. Michelle Lally, associate professor at Brown University (RI, USA) in an interview with BioPharmInsight.

Studies of Cervarix in Costa Rica that included a subpopulation of women who received only two doses of the vaccine suggest that antibody responses with two doses of Cervarix were almost as good as with three doses. However, this trial had a short follow-up period of four years and included a small number of women, Dr. Anne Szarewski from the Queen Mary University of London (UK) told BioPharmInsight. "Data from those who received two doses demonstrated that the vaccine elicits a response, but we do not know the duration of protection," she added.

The producers warn against any regimen of the vaccine other than what is in the product labeling, and at this time have no plans to seek

a two-dose indication, a GSK spokes person told the *Financial Times*.

Cervarix and Gardasil protect against two cancer causing HPV genotypes, HPV-16 and HPV-18, which account for 70% of cervical cancers. Gardasil contains in addition two HPV genotypes, HPV-6 and HPV-11, that are noncancerous but associated with 95% of genital warts. To further its reach in HPV, Merck is developing another vaccine, V503, which protects against five more cancer-causing HPV types than the two already contained in Gardasil. But recently Merck had to extend the late-stage human trial, comparing V503 to Gardasil, by one year, due to a lack of HPV infection seen among patients given Gardasil. This raises questions whether there is a need to protect against these additional HPV genotypes, which are less prevalent in the population.

Reference

1. Dorell C, et al. MMWR 2011; 60;1117-23.